REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. 103(a)

Claim 1 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Yaksh et al. (U.S. Patent No. 6,180,716; hereafter referred to as the '716 patent) and Heywood et al. (1988), and further in view of *Drug Facts and Comparisons* (1994). The Examiner has suggested that the '716 patent teaches that spinal (intrathecal/epidural) administration of centrally acting agents, such as anti-neoplastics and analgesics, have considerable therapeutic efficacy for treatment of pain, spasticity, central nervous system tumors, and infections, and further that methotrexate is one of these centrally acting agents that is given by intrathecal infusion. The Examiner further suggests that Heywood et al. (1998) teach that rheumatoid arthritis causes cervical spine instability and is a causative factor in symptoms of radiculopathy while *Drug Facts and Comparisons* (1994) teach administration of methotrexate for rheumatoid arthritis by ameliorating symptoms of inflammation

(pain, swelling stiffness). As a result, the Examiner suggests it would have *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to administer methotrexate intrathecally for treatment of lower back pain with radiculopathy because motivation is provided by the teaching of the '716 patent (teaching methotrexate intrathecally) and Heywood et al. (1988; teaching rheumatoid arthritis causes cervical spine instability and is a causative factor in symptoms of radiculopathy) combined with the teaching of *Drug Facts and Comparisons* (1994; teaching that methotrexate is routinely used to treat rheumatoid arthritis to ameliorate symptoms of inflammation). Applicants respectfully disagree with the Examiner's conclusions regarding the combination of cited references.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations.

At the outset, Applicants respectfully point out that the Examiner has failed to discuss the fact that a key limitation in the pending claim is related to the dose of methotrexate that is to be administered intrathecally in the method of the present invention. The claim recites a "1 mg/kg" dose is administered intrathecally. However, nowhere in the references cited by the Examiner is such a dose taught or suggested. In fact, the only reference that even mentions dosage of methotrexate is limited to oral dosing amounts (see page 1244 of *Drug Facts and Comparisons* 1994). There, the dosage taught is either a single oral dose of 12 mg/week, or a divided oral dose of 2.5 mg at 12 hour intervals for 3 doses given over the course of a week. Now, correcting that dose for the body weight in kg of a human (mg/kg), the unit of dosage claimed in the instant invention, a 12 mg dose in humans would be 12 mg divided by 60-70 kg body weight (average body weight of female and male humans) which is 0.2 mg/kg/week for a 60 kg human or 0.17 mg/kg/day for a 70 kg human, doses much lower than 1 mg/kg as now claimed. If one of skill was to correct the 2.5 mg dose for body weight, the range of doses in mg/kg would be even lower, 0.036 to 0.042 mg/kg. In particular in the case of methotrexate, a highly toxic drug (see discussion in *Drug Facts and Comparisons* 1994), one of skill in the art would not be able

to extrapolate an oral dose range to an intrathecal dose range, especially going higher in dose. Therefore, the combination of prior art references cited by the Examiner fails to teach or suggest each and every limitation of the claims as filed and cannot make obvious the invention of claim 1.

Moreover, a *prima facie* case of obviousness is established only when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Bell*, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). Thus, an obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). However, in the instant case, the statements made by the Examiner amount to no more than convenient assumptions about what would have been obvious to the skilled artisan at the time of the invention. However, under MPEP §2144.03, it is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based. *Zurko*, 258 F.3d at 1385, 59 USPQ2d at 1697. See also *In re Thrift*, 298 F.3d 1357, 1364, 63 USPQ2d 2002-2006 (Fed. Cir.

2002)(quoting Lee, 277 F.3d at 1344-45, 61 USPQ2d at 1435) (reliance on "common knowledge and common sense" do not fulfill the requirement to provide reasons in support of the findings of obviousness"). As a result, the Examiner's suggestion that it was *prima facie* obvious because all the claimed elements were known in the prior art is improper.

The '716 patent teaches that the problems associated with administration of drugs by routes such as intrathecal administration can be ameliorated by administering the drug in the form of a complex between the drug and a cyclodextrin. Therefore, although the patent mentions that drugs for treatment of pain or treatment of cancer can be administered intrathecally, nowhere does the patent teach or suggest that it is advisable to do so without first complexing drugs using their invention. In fact, the patent discusses that the problems associated with administration of drugs intrathecally, including a drug such as methotrexate, is the problem of toxicity (see column 1, lines 39-56). Then at column 8, lines 66-68, through column 9, lines 1-8, it is specifically taught that "Combinations of methotrexate and a cyclodextrin could alter favorably the redistribution kinetics after intrathecal or neuraxial administration." Clearly, this patent is teaching one of skill that methotrexate intrathecally,

by itself, is not an optimal therapeutic application of the drug. The paper of Heywood et al. (1988) teaches only that rheumatoid arthritis was associated with radiculopathy in one of 26 patients described. None of the other cases discussed (25 other patients) is described as being suffering from radiculopathy. Then, *Drug Facts and Comparisons* (1994) is merely a textbook that lists facts about methotrexate. Methotrexate is listed as being a drug used to treat rheumatoid arthritis. However, radiculopathy and intrathecal administration are not taught or even suggested by this text, while the text teaches use of much lower doses of methotrexate than are claimed in the instant invention, by a different route (orally), for treatment of rheumatoid arthritis. As a result, it is mere speculation on the part of the Examiner that one of skill would arrive at motivation or an expectation of success in making the invention of claim 1 by combining the teaching of the '716 patent, which points one of skill to use of methotrexate intrathecally only in combination with a cyclodextrin, with the teaching of Heywood et al. (1988), which teaches that in one of 26 patients with rheumatoid arthritis radiculopathy was seen, with the teaching of *Drug Facts and Comparisons* (1994), which fails to mention treatment of radiculopathy at any dose and teaches treatment of symptoms of

arthritis orally only at much lower doses. Nowhere does this combination of prior art references provide one of skill with any working example of using methotrexate intrathecally for treatment of pain with radiculopathy at any dose, including the dose claimed. Accordingly, this combination of prior art references cannot establish a *prima facie* case of obviousness and withdrawal of this rejection is respectfully requested.

II. Conclusions

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **February 18, 2009**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053
856-810-1515
Email: JMLicata@licataandtyrrell.com